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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/989,130	11/21/2001	Richard W. Titball	3974-3	1328

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/30/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/989,130	TITBALL ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *08/894,527* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' preliminary amendment filed 11-21-01 and response to "Restriction Requirement" filed 3-27-03 have been entered. Claims 1-31 have been canceled. Claims 32-38 have been added. After further consideration of the claimed subject matter, the "Restriction Requirement" of claims 32-38 mailed 1-27-03 (Paper No. 4) has been withdrawn. Claims 32-38 are pending and under consideration.

Claim Objections

The term "CLAIMS" on the first claim page, i.e. page 21, is improper. Changing the term "CLAIMS" to "We claim:", "I claim:", or "What is claimed is:" would be remedial.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 32-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Claim 32 is directed to a pharmaceutical composition comprising an antibody conjugated to a lipase or a lipase component, such as N- or C-terminal recombinant CPAT, having no or less lipase activity as compared to lipase holoenzyme and a pharmaceutically acceptable carrier,

diluent or excipient. Claims 33 and 36 are directed to a pharmaceutical composition comprising a pharmaceutical agent protected in a liposome that is associated with or integrally contains a second lipase component able to reconstitute lipase activity when contacted with a first lipase component bound to an antibody. Claim 36 specifies the first or second lipase component is N-terminal recombinant CPAT or C-terminal CPAT. Claims 34 and 37 are directed to a pharmaceutical package comprising the pharmaceutical composition of claim 32 and a pharmaceutical composition comprising a pharmaceutical agent protected in a liposome. Claims 35 and 38 are directed to a pharmaceutical package comprising the pharmaceutical compositions of claims 32 and 33.

The specification of the present application discloses the enhanced killing of HeLa cells using anti-CEA-phospholipase C conjugate in conjunction with drug liposomes *in vitro*. A pharmaceutical composition is a composition which implies *in vivo* applicability such that therapeutic effects against a disease or a disorder are obtained. The claims read on a therapy of using a reconstituted lipase activity by combining two or more lipase components *in vivo* so as to lyse a lipid structure such as liposome and release a pharmaceutical agent, including any small organic molecule, a polynucleotide sequence, a protein, and an antibody, from said lipid structure for the treatment of a particular disease or disorder. The claims encompass using a pharmaceutical composition for gene therapy, protein therapy, immunotherapy and organic compound therapy *in vivo*.

The specification fails to provide adequate guidance and evidence for how to administer the claimed pharmaceutical composition containing a pharmaceutical agent, such as a small organic molecule, a polynucleotide sequence, a protein, or an antibody, via various

administration routes so as to provide therapeutic effect for the treatment of a particular disease or disorder *in vivo*. The specification also fails to provide an adequate guidance for the correlation of the pharmaceutical agent with a specific disease or a disorder such that said pharmaceutical agent could provide therapeutic effects for said specific disease or disorder *in vivo*.

The nature of the invention being gene therapy, the state of the prior art was not well developed and was highly unpredictable at the time of filing. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82).

In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract). Verma et al. states that one major obstacle to success has been the inability to deliver genes efficiently and obtain sustained expression (see Verma et al., page 239, col. 3). Similarly, the delivery route of a protein or an antibody, the amount and stability of the protein or antibody present at the targeted site, and the uptake of the protein or antibody by the targeted cells and its activity within the targeted cells are all important factors for a successful protein therapy or immunotherapy.

Further, there is no evidence of record that whether delivery of a first pharmaceutical composition containing an antibody conjugated to a lipase or a lipase component and a second pharmaceutical composition containing a liposome associated with a lipase component to a targeted site via various administration routes could provide sufficient pharmaceutical agents, including polynucleotides, organic compounds, proteins and antibodies, at the targeted site so as to provide therapeutic effect for a particular disease or disorder *in vivo*. In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to use the claimed pharmaceutical composition for gene therapy, protein therapy, immunotherapy, or organic compound therapy *in vivo*.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the working examples provided, and the breadth of

the claims that it would require a skilled artisan at the time of the invention to engage in undue experimentation to practice over the full scope of the invention claimed.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claim 32 is rejected under 35 U.S.C. 102(b) as being anticipated by Flickinger et al., 1976 (Europ. J. Cancer, Vol. 12, pp. 159-160).

Claim 32 is directed to a pharmaceutical composition comprising an antibody conjugated to a lipase or a lipase component, such as N- or C-terminal recombinant CPAT, having no or less lipase activity as compared to lipase holoenzyme and a pharmaceutically acceptable carrier, diluent or excipient.

Flickinger teaches preparation of conjugates of phospholipase C to tumor antibodies and dialyzed the conjugates against sterile Earles saline to ascertain the cytotoxic effect upon the homologous tumor cells (e.g. p. 159). The Earles saline is considered a pharmaceutically acceptable carrier, diluent or excipient. Thus, claim 32 is anticipated by Flickinger.

5. Claim 34 is rejected under 35 U.S.C. 102(b) as being anticipated by Harris, 1984 (US Patent No. 4,463,090).

Claim 34 is directed to a pharmaceutical package comprising the pharmaceutical composition of claim 32 and a pharmaceutical composition comprising a pharmaceutical agent protected in a liposome.

Harris teaches an enzyme immunoassay using a complex containing a phospholipase or lipase coupled to an antibody and adding liposomes containing an enzyme, a proenzyme or a coenzyme, such as alkaline phosphatase or peroxidase, to said complex such that the liposomes are lysed by the lipase to release the enzyme etc. in the liposomes (e.g. column 8, 9). The buffers containing the lipase-antibody complex and the liposomes are considered pharmaceutically acceptable carriers. The enzyme, a proenzyme or a coenzyme, such as alkaline phosphatase or peroxidase, is considered a pharmaceutical agent. Thus, claim 34 is anticipated by Harris.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.